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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,805	01/19/2005	Andrew Lennard Lewis	Q83534	5416

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EXAMINER
PURDY, KYLE A

ART UNIT	PAPER NUMBER
1611	

NOTIFICATION DATE	DELIVERY MODE
11/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/506,805	LEWIS ET AL.	
	Examiner	Art Unit	
	Kyle Purdy	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 7-12, 20, 24-35, 38, 48, 45-58 and 61* is/are pending in the application.

4a) Of the above claim(s) *29-35 and 45-56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,7-12,20,24-28,38,42,57,58 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application

1. The Examiner acknowledges receipt of the amendments filed on 07/21/2009 wherein claims 1, 57 and 58 have been amended and claim 61 is newly added. Claims 13-16, 21-23, 43, 44, 59 and 60 have been cancelled.

2. Claims 1, 7-12, 20, 24-28, 38, 42, 57, 58 and 61 are presented for examination on the merits. The following rejections are made.

Response to Applicants' Arguments

3. Applicants arguments filed 07/21/2009 regarding the rejection of claims 13-16, 21-23, 43, 44, 59 and 60 made by the Examiner under 35 USC 103(a) over Lobb et al. (JACS, 2001) in view of Kataoka et al. (Adv. Drug Delivery Rev., 2001), evidenced by Dalmark et al. (J Gen. Physiol., 1981) have been fully considered and they are found persuasive. This rejection has been overcome by cancellation of the claims.

4. Applicants arguments filed 07/21/2009 regarding the rejection of claims 1, 7-12, 24-28, 38, 57 and 58 made by the Examiner under 35 USC 103(a) over Lobb et al. (JACS, 2001) in view of Kataoka et al. (Adv. Drug Delivery Rev., 2001), evidenced by Dalmark et al. (J Gen. Physiol., 1981) have been fully considered but they are not found persuasive.

5. Applicants arguments filed 07/21/2009 regarding the rejection of claims 20 and 42 made by the Examiner under 35 USC 103(a) over Lobb et al. (JACS, 2001) in view of Kataoka et al. (Adv. Drug Delivery Rev., 2001) and Coessens et al. (Prog. Poly. Sci., 2001), evidenced by Dalmark et al. (J Gen. Physiol., 1981) have been fully considered but they are not found persuasive.

6. The rejection of claims 1, 7-12, 20, 24-28, 38, 42, 57 and 58 made by the examiner under 35 USC 103(a) is **MAINTAINED** for the reasons of record in the office action mailed on 04/21/2009.

7. In regards to the 103(a) rejection, Applicant asserts the following:

A) As indicated in Example 7, diisopropylamino ethyl methacrylate (DPA) exhibits improved properties over diethylaminoethyl methacrylate (DEA herein);

B) The core of the DPA micelles is more conducive to pyrene uptake than DEA micelles;

C) OeGBr is a hydrophilic polymer, not hydrophobic as the Examiner suggests. Moroever, claim 57 requires the initiator be hydrophobic; and

D) Kataoka would not provide sufficient motivation to include doxorubicin into the micelle of Lobb. The polymers of Kataoka are wholly dissimilar from those of Lobb.

8. In response to A, the Examiner acknowledges Example 7 and the results shown. It's noted that micelles do not form at a pH of 7.4 while incubated at 5° and 70°C. However, at 25°C, a more relevant temperature, a temperature more similar to that of room and the body, micelles readily form at a pH of 7.4. It's unclear to the Examiner how forming micelles at a physiological pH under frigid or hot conditions is an improvement over readily forming micelles at a temperature more indicative of a natural working environment, as well as indicative of body temperature, which is the ultimate intended use of these micellar preparations. It's unclear how such results would have been unexpected and how said results would have provided a significant, practical advantage. See MPEP 716.02(a).

9. In response to B, it is not surprising that Applicants has found that DEA cores are less hydrophobic than DPA cores. Any person of ordinary skill in the art would readily recognize

that isopropyl is a larger and slightly more hydrophobic functional group than ethyl. As such, a DPA micelle core would be expected to be more hydrophobic and larger than a DEA core. Would it have been surprising if Applicant found that a propyl functionality exhibited better drug uptake properties? No, because that core would have been expected to be larger and more hydrophobic than the ethyl core. Similarly, would it have been surprising if a methyl side group exhibited less ability to absorb hydrophobic molecules? Again, no because methyl functional groups are smaller and less hydrophobic than ethyl functional groups. A core containing only methyl functional groups would be expected to be smaller and less hydrophobic than that of the ethyl core, thus the methyl core would be expected to hold less drug than the ethyl core. Based on a simple scientific understanding, any ordinarily skilled person would readily envisage such properties which Applicant is currently stating are unexpected. Such results would have been apparent by addition or removal a methyl to the ethyl side chain of the polymer taught by Lobb. Applicants arguments are not found persuasive.

10. In response to C, the Examiner acknowledges that OgGBr is hydrophobic, not hydrophilic. The Examiner must have erred in typing. Regardless, OeGBr is being used as an initiator to catalyze the radical transfer polymerization process, and is not acting as the hydrophilic component of the block copolymer. With respect to Applicants assertion that the claim 57 requires a hydrophobic initiator, this is not clear from the claim language. Claim 57 states, "wherein the polymerization is an atom transfer radical polymerization or group transfer polymerization carried out in the presence of an atom transfer or group transfer initiator that is a polymer compound in which the polymeric moiety is hydrophobic and forms the hydrophobic block of the copolymer". The polymeric moiety could be the initiator; however, it could also be

the hydrophobic monomers being polymerized to form the hydrophobic block of the copolymer as stated later in the claim. If Applicant intends their initiator to be hydrophobic, then Applicant should clearly claim it as such.

11. In response to D, it's duly noted that Lobb teaches different polymers from that of Kataoka. However, this does not preclude their combination. Lobbs teaches amphiphilic copolymers that form micelles wherein the hydrophilic portion of the copolymer is present on the outer surface of the micelle and the hydrophobic portion is present in the core of the micelle when present in aqueous systems. Lobb teaches that these micelles have substantial promise in drug delivery applications, but fails to expand on such promise. Kataoka is relied upon for the showing that block amphiphilic copolymer micelles, like those taught by Lobb (structurally), are commonly employed in drug delivery systems, and are especially useful for the delivery of hydrophobic drugs such as doxorubicin. Thus, based upon the suggestion by Lobb that their nanoparticles have substantial promise for applications in drug delivery, any person of ordinary skill in the art would look to the art for teachings centered around using amphiphilic micelles for the delivery of drugs. If such a result were the combination of Lobb and Kataoka to arrive at a composition as presently claimed, then such a result would be a product of ordinary skill and common sense, not one off innovation. Applicants argument is not found persuasive.

Maintained Rejections, of Record (claims 1, 7-12, 20, 24-28, 38, 42, 57 and 58) and New Rejections, Necessitated by Amendment (claim 61)

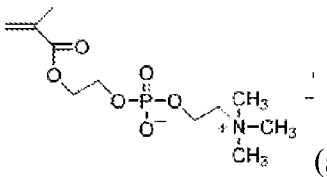
Claim Rejections - 35 USC § 103

12. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

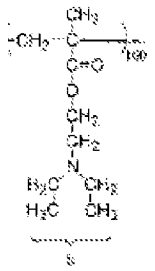
13. **Claims 1, 7-12, 24-28, 38, 57, 58 and 61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lobb et al. (J. Am. Chem. Soc., 2001. 123, 7913-7914; of record) in view of Kataoka et al. (Adv. Drug Delivery Rev., 2001, 47(1), 113-131; of record), evidenced by Dalmark et al. (J. Gen. Physiol, 1981, 78, 349-364; of record).**

14. Lobb discloses the synthesis of a biocompatible phosphrylcholine-based methacrylate copolymer. The copolymer is an amphiphilic block copolymer having a hydrophilic block and in the solution, and a biologically active compound associated with the polymer [fibrinogen] (see page 7914, left column 2nd paragraph; see instant claim 1), wherein the hydrophilic block has pendant zwitterionic groups (see Figure 2; structure; see instant claim 1). The copolymer is in the form of micelles (see Figure 2, 'DEA core micelles'; see instant claim 1). The hydrophilic block is formed by radical polymerization of the ethylenically unsaturated monomers (see page 7913, left column, 2nd paragraph; see instant claim 1). The hydrophilic monomers comprise a zwitterionic monomer having the following structure:



(see Figures 1 and 2; see instant claim 6-12 and 38).

15. The hydrophobic block comprises a pendant group which is ionizable and possesses a pKa or pKb in the range of 4 to 10 (see Figure 2, structure). The hydrophobic structure is shown below:



16. The pKa for the hydrophobic structure is 9.17 (see STN search of structure b; see instant claim 13). The hydrophobic block is polymerized by radical polymerization of the ethylenically unsaturated monomers (see page 7914, left column, 4th paragraph). The degree of polymerization for the hydrophilic block is 30 (see Figure 2, structure;) and the degree of polymerization for the hydrophobic block is 100 (see Figure 2, structure). The ratio for the degrees of polymerization is 10:3 which falls within the range of 1:5 to 10:1 (see Figure 2, structure). The polymerization process for polymerizing the hydrophilic block is via atom transfer radical polymerization (see page 7913, left column, 2nd paragraph; see instant claims 24-25). Lobb teaches that the atom transfer radical polymerization initiator is that of oligo(ethylene glycol) bromide (OEGBr). OEGBr is a hydrophobic polymer compound and is taught to be used for the sysnthesis of the MPC homopolymer (see page 7913, right column, 2nd paragraph; see instant claim 26). It is also taught that that MPC diblock copolymers can also be synthesized via atom transfer radical polymerization (see page 7914, left column, 4th paragraph; see instant claims 24 and 25). Moreover, Lobb suggests that the polymeric micelles are highly biocompatible and show considerable promise for drug delivery applications (see 7914, right column).

17. Lobb fails to specifically teach the species of diisopropylamino ethyl phosphate inner salt. Lobb also fails to teach the nanoparticle as having a hydrophobic drug associated with the

core of the nanoparticle, said drug having a partition coefficient between octanol and water of at least 1.5.

18. Kataoka is a review article directed to block copolymer micelles and their use in local drug delivery. In the abstract it is taught that block copolymers are useful because of the fact that the outer hydrophilic surface can be functionalized to optimize its physiochemical and biological properties whereas the inner hydrophobic core is useful as a functioning reservoir for a variety of diverse drugs. It is also taught that much interest has been directed to loading nanoparticles with drugs because of the relatively high loading capacity of the inner core (see page 114, left column). In section 2, an example of an amphiphilic copolymer micelle is taught wherein the micelles hydrophobic core houses the cytotroxic drug doxorubicin (see page 115). Doxrubicin has a partition coefficient between water and octanol of 1.9 (see Dalmark et al., page 356; see instant claim 1) It is taught that significant pi-pi interactions contribute substantially to increasing the cohesive force in the core which stabilizes the physically entrapped drug (see page 116, left column).

19. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Lobb and Kataoka with a reasonable expectation for success in arriving at a composition comprising an amphiphilic copolymer having a zwitterionic group which has a biologically active, cytotoxic molecule with a partition coefficient of at least 1.5 sequestered in the core of the micelle. One would have been motivated to substitute diisopropylamino ethyl methacrylate for (diethylamino)ethyl methacrylate because the two monomers only differ by the presence of a methyl group. The presence of a methyl group in place of a hydrogen does not give patentable momentum to the recited species. It is well

established that a methyl is structurally analogous to a hydrogen, and absent any secondary result, the elected species would possess the same functional properties as that of diiethylammonium. With respect to including the drug within in the core of the particle, this is also obvious. Kataoka specifically teaches that loading hydrophobic cytotoxic drugs which have a partition coefficient of at least 1.5 into their core is a common practice in the art of amphiphilic micelles. One would be motivated to employ the structure discussed by Kataoka because of the ability to achieve high loading of drug into the particle which means high localized dosages to the patient. Moreover, by loading the drug into the core of the micelle, the drugs rate of release will be controlled and the drug will provided a thermodynamically stable environment. With respect to the requirement that the copolymer be synthesized by an initiator (e.g. OEGBr) possessing a hydrophobic polymer moiety is also obvious, as it is specifically suggested by Lobb. Therefore, the invention as a whole is *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in absence of evidence to the contrary.

20. Note, Dalmark is cited as to show that doxorubicin has a partition coefficient between octanol and water of at least 1.5.

21. **Claims 20 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lobb et al. (J. Am. Chem. Soc., 2001. 123, 7913-7914; of record) in view of Kataoka et al. (Adv. Drug Delivery Rev., 2001, 47(1), 113-131) and Coessens et al. (Prog. Poly. Sci., 2001, 26, 337-377; of record), evidenced by Dalmark et al. (J. Gen. Physiol, 1981, 78, 349-364).**

22. Lobb, Kataoka and Dalmark are relied upon for disclosure described in the rejection of claim 1 under 35 U.S.C. 103(a).

23. Lobb teaches that the polydispersity of the MPC homopolymer block is from between 1.23 to 1.45 (see page 7914, left column, 2nd paragraph).

24. Lobb, Kataoka and Dalmark fail to teach the polydispersity for the hydrophobic block of the copolymer.

25. Coessens cures this deficiency. Coessens is drawn to describing in detail the properties generally associated with atom transfer radical polymerization process, teaches that atom transfer radical polymerization creates well-defined, precisely controlled polymers with polydispersities generally lower than 1.3 (see Coessens, page 339, last paragraph).

26. Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Lobb, Kataoka, Coessens and Dalmark with a reasonable expectation for success in arriving at a composition comprising an amphiphilic block copolymer having a hydrophilic and a hydrophobic block, dispersed in solution, and a biologically active compound associated with the polymer, wherein the hydrophilic block as pendant zwitterionic groups wherein the polydispersity of molecular weight of each block is from 1.1 to 1.4. Although Lobb is silent to the polydispersity of the hydrophobic block, the block if synthesized by atom transfer radical polymerization would quite likely have a polydispersity less than 1.3. Therefore, the invention as a whole is *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Conclusion

27. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

28. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

29. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kyle A. Purdy whose telephone number is 571-270-3504. The examiner can normally be reached from 9AM to 5PM.

30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau, can be reached on 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

31. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Kyle Purdy/

Examiner, Art Unit 1611
November 3, 2009

/David J Blanchard/
Primary Examiner, Art Unit 1643